Prevalence of Perioperative Asymptomatic Proximal Deep Vein Thrombosis in Thai Gynecologic Cancer Patients

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Background: *Thromboprophylaxis of deep vein thrombosis in gynecologic cancer surgery in Thai patients is not routinely performed.*
Objective: *The prevalence of perioperative asymptomatic proximal deep vein thrombosis of 100 patients with gynecologic cancer was identified.*
Material and Method: *Duplex ultrasonography of proximal vein of legs was performed in each patient, seven to 14 days, before and after surgery.*
Results: *The prevalence of perioperative asymptomatic proximal deep vein thrombosis was 7%. The prevalence of preoperative asymptomatic proximal deep vein thrombosis of legs was 5% and postoperative incidence of asymptomatic proximal deep vein thrombosis of legs was 2.11%. Acute symptomatic pulmonary embolism was found in only one patient. All patients who developed deep vein thrombosis had adenocarcinoma of ovary or uterus, but not cervical cancer. The other risk factors of venous thromboembolism were comparable between deep vein thrombosis and non-deep vein thrombosis group.*
Conclusion: *The patients with adenocarcinoma of ovary and uterus seem to be the greatest risk of perioperative deep vein thrombosis. High prevalence of venous thromboembolism in gynecologic cancer surgery of Thai patients should be concerned.*

Keywords: *Asymptomatic disease, Deep vein thrombosis, Female genital neoplasms, Perioperative period, Prevalence*

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Venous thromboembolism (VTE) is one of the most common postoperative complications observed among Caucasian population[1]. The prevalence of asymptomatic deep vein thrombosis (DVT) in Western population ranges from 15% to 40% in patients undergoing major general surgery and gynecologic surgery without thromboprophylaxis. The rate of perioperative fatal pulmonary embolism (PE) ranges from 0.2% to 0.9%[2]. However, VTE has been regarded as a rare disease among Asian population[3,4]. The long belief that VTE is rare in Asian patients has been challenged by many studies. An incidence of perioperative DVT in Asian patients undergoing general surgery ranges from 3% to 28% which is lower than those reported for the Caucasian[5]. In addition, some authors reported that the incidence of VTE among Asian patients had increased[6,7].

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Gynecologic cancer patients have a particularly high thrombosis risk[8]. From the retrospective study, the authors found that gynecologic malignancies were the most common cancer which were associated with acute DVT among Thai patients[9]. The presence of malignancy created the 4-fold increase in the incidence of VTE following gynecologic surgery[10]. The prevalence of DVT in gynecologic cancer patients ranges from 11 to 18% with the rate of pulmonary embolism (PE) between 1 and 2.6%[11-13]. However, perioperative medical thromboprophylaxis for gynecologic cancer in most Thai patient has been neglected. Most patients have not been received anticoagulant during the operation.

Because most fatal acute pulmonary embolism usually occurs from asymptomatic leg thrombus especially in the proximal vein such as popliteal vein and femoral vein[14], it is important to investigate the prevalence and risk factors for asymptomatic DVT of the proximal vein. The aim of this present study was to evaluate prevalence of asymptomatic acute proximal DVT by duplex ultrasound during the perioperative

period of gynecologic malignancy in Thai patients who did not receive VTE prophylaxis.

Material and Method

This prospective descriptive study aimed to demonstrate the prevalence of acute asymptomatic deep vein thrombosis and its risk factors in perioperative gynecologic cancer patients. One hundred patients attending Siriraj hospital, Bangkok, Thailand between January 2011 and May 2012 for their gynecologic cancer surgery were enrolled for this study. Once the informed consent was obtained, the patients were interviewed for clinical information. Demographic data was collected including: age, sex, height, weight, body mass index (BMI), previous diagnosis, treatment of DVT and PE, history of irradiation and chemotherapy, family history of VTE, recent immobilization of lower extremities (more than 3 days), recent surgery within three months, recent trauma within three months, recent admission of severe medical illness, other associated cancers, varicose vein, thrombophilia, use of contraceptive pills, hormonal therapy, cardiac diseases, and cerebrovascular disease.

Each participant underwent DVT screened by color Doppler duplex ultrasound examination with venous compression test, augmentation, color Doppler filling in the veins and respiratory phase variation in common femoral veins, and popliteal veins to diagnose proximal DVT prior to surgery[15]. The color Doppler duplex ultrasonography was performed on GE LOGIC 9, (GE Healthcare, USA) using 5 to 10 MHz linear transducers by an experienced vascular surgeon.

If proximal DVT was detected, the patients received anticoagulant immediately and the surgery was postponed for two to four weeks. After surgery, the patients received postoperative anticoagulant following standard guideline[16]. If the preoperative duplex scan screening was negative for proximal DVT, the patients underwent cancer surgery without VTE prophylaxis.

The patients who developed symptoms and signs of either acute DVT or acute PE after surgery were investigated by duplex ultrasonography or computed tomography angiography (CTA) pulmonary immediately.

After surgery for seven to 14 days, all asymptomatic patients were screened by duplex ultrasound to detect postoperative acute proximal DVT.

The participants with negative duplex scan in preoperative and postoperative period were telephone-interviewed at one and three months postoperatively to inquire about any clinical VTE that subsequently developed to the duplex ultrasonography.

Hospital medical records were reviewed for the following information: site of cancer, type of cancer, staging of cancer and type of operation.

A sample size of 100 participants was calculated based on an estimated 40% incidence of VTE, using a precision 10% with the level of confidence of 95%[2].

Descriptive data analysis was presented in number, percentage, median, mean, and standard deviation. For data comparison between groups, Chi-square test and Student's t-test were used for discrete variables and continuous variables. A p-value <0.05 was considered to be statistically significant. Statistical analysis was done using PASW Statistics 18.0 software.

The present study protocol and informed consent were approved by the Institutional Review Board, and all the patients gave informed consent.

Results

Patient characteristics

There were 100 female patients enrolled in the study. All of the patients had gynecologic cancer and were planned for surgical treatment. Mean age of the patients was 54.38 (SD ±11.4) years. Mean BMI was 24.49 (SD ±4.35) kg/m^2. Mean duration of hospital stay was 8.63 (SD ±4.94) days. No patients had chest symptoms including chest pain, dyspnea, hemoptysis and symptoms of deep vein thrombosis prior to surgery. No patients received any treatment for VTE prior to enrollment.

The most common presenting symptoms were abnormal vaginal bleeding followed by abdominal mass (Table 1). The most common site of cancers in the present study was endometrial cancer (42%), followed by ovarian cancer (26%), cervical cancer: adenocarcinoma (16%) and cervical cancer: squamous cell carcinoma (16%) (Table 1).

Characteristics of cases of perioperative acute proximal deep vein thrombosis

Five patients had acute asymptomatic proximal DVT found during the screening duplex ultrasound prior to surgery. Therefore, the prevalence of DVT prior to surgery was 5% (5 cases of 100 cases)

Among five cases of pre-operative proximal DVT, three cases were diagnosed as ovarian cancer and two cases were endometrial cancer. According to the site of acute proximal DVT, two cases had right femoropopliteal DVT, one case had left femoropopliteal

DVT, one case had bilateral femoropopliteal DVT, and one case had right popliteal DVT and left femoropopliteal DVT.

There were two cases of post-operative DVT; one had ovarian cancer and had left femoropopliteal DVT. Another had endometrial cancer and had right popliteal DVT (Table 2). The incidence of postoperative asymptomatic proximal DVT was 2.11% (2 cases of 95 cases). Both cases of postoperative DVT were operated in supine position.

All seven cases of perioperative acute proximal DVT were asymptomatic. The authors found only one case of symptomatic acute pulmonary embolism associated with acute asymptomatic proximal DVT of lower extremities. In addition, the authors found that all seven cases of acute perioperative proximal DVT were gynecologic adenocarcinoma (Table 2).

Other patients who did not have perioperative proximal DVT were interviewed by telephone at one-month and three-month postoperatively. No one had symptoms of VTE.

Table 1. Presenting symptoms, sites and histological type of cancer of 100 gynecologic cancer patients

	n (%)
Chief complaint	
Vaginal bleeding	51 (51.0)
Pelvic mass	9 (9.0)
Abnormal pap smear	8 (8.0)
Abdominal pain	7 (7.0)
Ascites	2 (2.0)
Site and histology of cancer	
Cervical cancer (SCC)	16 (16.0)
Cervical cancer (Adeno CA)	16 (16.0)
Ovarian cancer (Adeno CA)	26 (26.0)
Endometrial cancer (Adeno CA)	41 (41.0)
Carcinomatosis peritonei	1 (1.0)

SCC = squamous cell carcinoma; Adeno CA = adenocarcinoma

Comparing between acute perioperative proximal DVT and non DVT group

Risk factors of venous thromboembolism were compared between DVT and non-DVT groups (Table 3). There were no statistical differences in all risk factors between DVT and non-DVT groups.

Discussion

Perioperative VTE prophylaxis for Asian patients is usually neglected by most physicians. Some reports exhibited the high prevalence[5]; however, the others showed that VTE in Asian population were rare[17]. In addition, perioperative unexpected death was reported frequently in cancer surgery patients without definite etiology. Acute pulmonary embolism in these patients was reported as the silent killer. No previous clinical research was performed to identify the exact prevalence and risk factor of DVT in gynecologic malignancy surgery in Asia.

The present study, the authors prospectively observed the prevalence of perioperative acute asymptomatic proximal DVT of patients with gynecologic cancer patients who did not receive medical thromboprophylaxis for VTE. The authors found that the total prevalence of perioperative asymptomatic proximal DVT was 7%, the preoperative 5% and the postoperative 2.1%. Symptomatic pulmonary embolism was observed in one case of postoperative asymptomatic proximal DVT.

From the results, all perioperative proximal DVT had no symptom and sign of acute DVT at the time of diagnosis. It is very dangerous to perform surgery in the proximal DVT patients without medical VTE prophylaxis. It is also dangerous to observe and

Table 2. Characteristic cases of perioperative acute asymptomatic proximal DVT

Case	Age	Time of Dx	Organ	Type	Staging	Site of DVT	Symptomatic PE
1	56	Pre-op	Ovary	Adeno CA	IV	Bilateral CFV + Pop V	No
2	51	Pre-op	Ovary	Adeno CA	I	Rt CFV + Pop V	No
3	68	Pre-op	Ovary	Adeno CA	I	Lt CFV + Lt Pop V	No
4	56	Pre-op	Endometrium	Adeno CA	III	Lt CFV + Bilat Pop V	Yes
5	55	Pre-op	Endometrium	Adeno CA	III	Rt Pop V	No
6	80	Post-op	Ovary	Adeno CA	III	Lt CFV + Pop V	No
7	65	Post-op	Endometrium	Adeno CA	I	Rt Pop V	No

DVT = deep vein thrombosis; Dx = diagnosis; PE = pulmonary embolism; Pre-op = preopearative; Post-op = postoperative; Adeno CA = adenocarcinoma; CFV = common femoral vein; Pop V = popliteal vein; Rt = right; Lt = left

Table 3. Comparing risk factors between DVT group and non-DVT group

Risk factors	DVT (n = 7), n (%)	Non-DVT (n = 93), n (%)	p-value
Family history of VTE	0 (0)	1 (1.1)	1.000
Recent immobilization (>3 days)	0 (0)	1 (1.1)	1.000
Previous radiation	0 (0)	8 (8.6)	0.547
Previous chemotherapy	1 (14.3)	17 (18.3)	0.631
Recent surgery (<3 month)	1 (14.3)	3 (3.2)	0.225
Recent trauma (<3 month)	0 (0)	2 (2.2)	0.864
Recent admission of severe medical illness	1 (14.3)	2 (2.2)	0.197
Other malignancy	0 (0)	6 (6.5)	0.639
Varicose vein	3 (42.9)	18 (19.4)	0.159
Contraceptive pills/hormone	1 (14.3)	16 (17.2)	0.606
Vascular disease in family	1 (14.3)	4 (4.3)	0.310

VTE = venous thromboembolism

wait for VTE treatment until the symptoms and signs of acute DVT and acute PE occur.

According to recent VTE practice guideline, the prevalence of perioperative VTE in the gynecologic cancer patients who do not receive anticoagulant for VTE prophylaxis is 6% or more[1]. These patients are classified as high-risk for perioperative VTE development. Combined medical and mechanical thromboprophylaxis is required[1]. Gynecologic cancer surgery in Thai patients is classified as high risk operation for VTE because the prevalence of VTE from the present study was 7%.

According to the risk factors for perioperative VTE which were reported in previous literature, we found that the risk factors including family history of VTE, recent immobilization (>3 days), previous irradiation, previous chemotherapy, recent surgery (<3 months), recent trauma (<3 months), recent admission of severe medical illness, associated other malignancy, varicose vein, use of contraceptive pills and hormone, vascular disease in family were comparable between DVT and non DVT groups. Therefore, these risk factors did not increase risk of VTE in gynecologic cancer surgery patients. Moreover, we found that acute DVT and PE occurred in patients with adenocarcinoma of ovary and uterus only, not cervix. As a result, the patients with adenocarcinoma of ovary and uterus seem to have the greatest risk of perioperative VTE.

Duplex ultrasound is a common test of acute DVT because it is noninvasive. The sensitivity of duplex ultrasound for asymptomatic proximal (femoral and popliteal) DVT is up to 95%[18].

The present study's result might make the physician concerned about the high prevalence of perioperative VTE in gynecologic cancer surgery in Thai patients. The usefulness of routine preoperative and seven to14 day postoperative duplex scan in Thai patients to detect proximal DVT should be evaluated in the future clinical research. Moreover, routine thromboprophylaxis of VTE in Thai patients performing gynecologic cancer surgery should be investigated in randomized controlled trial.

Conclusion

High prevalence of venous thromboembolism in gynecologic cancer surgery of Thai patients should be concerned. The patients with adenocarcinoma of ovary and uterus seem to be the greatest risk of perioperative VTE.

What is already known on this topic?

The prevalence of asymptomatic perioperative proximal deep vein thrombosis is very high in gynecologic cancer surgical patients in Europe and USA. The patients must receive prophylaxis of venous thromboembolism by anticoagulant before and after surgery.

What this study adds?

The prevalence of venous thromboembolism in gynecologic cancer surgery of Thai patients is also high, although it is less than the prevalence of venous thromboembolism in Western countries. The patients with adenocarcinoma of ovary and uterus seem to have the greatest risk of perioperative deep vein thrombosis.

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Potential conflicts of interest

None.

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ความชุกของภาวะลิ่มเลือดอุดหลอดเลือดดำชั้นลึกของขาในผู้ป่วยสตรีไทยที่มารับการผ่าตัดรักษามะเร็งในระบบอวัยวะสืบพันธุ์

ณัฐวุฒิ เสริมสาธนสวัสดิ์, รัตนา เพียรเจริญสิน, เกียรติศักดิ์ หงษ์คู, ชุมพล ว่องวานิช, เฉนียน เรืองเศรษฐกิจ, คามิน ชินศักดิ์ชัย, ชัยรัตน์ ลีลาพัฒนดิษฐ์, สุวนิตย์ ธีระศักดิ์วิชยา, ประมุข มุทิรางกูร

ภูมิหลัง: *ในประเทศไทยยังไม่มีการให้ยาในการป้องกันภาวะลิ่มเลือดอุดหลอดเลือดดำชั้นลึกของขาในผู้ป่วยมะเร็งนรีเวชทุกคนที่เข้ารับการรักษาโดยการผ่าตัด*

วัตถุประสงค์: *หาความชุกของการเกิดภาวะลิ่มเลือดอุดหลอดเลือดดำชั้นลึกของขาที่ไม่แสดงอาการในผู้ป่วยมะเร็งนรีเวช 100 รายที่เข้ารักษาโดยการผ่าตัด*

วัสดุและวิธีการ: *ผู้ป่วยทุกรายจะได้รับการตรวจด้วยเครื่องอัลตราซาวด์ดูเพล็กซ์ ทั้งระยะก่อนผ่าตัดและหลังผ่าตัด 1-2 สัปดาห์*

ผลการศึกษา: *ความชุกของการเกิดภาวะลิ่มเลือดอุดหลอดเลือดดำชั้นลึกของขาที่ไม่แสดงอาการในระยะก่อนและหลังผ่าตัดรวมกัน ร้อยละ 7 โดยที่ตรวจพบในระยะก่อนผ่าตัด ร้อยละ 5 และตรวจพบอุบัติการณ์หลังผ่าตัด ร้อยละ 2 มีผู้ป่วยหนึ่งรายที่แสดงอาการเหนื่อยหอบจากลิ่มเลือดที่อุดที่ขาได้หลุดไปอุดหลอดเลือดแดงที่ปอด ผู้ป่วยทุกรายที่เป็นภาวะลิ่มเลือดอุดหลอดเลือดดำชั้นลึกของขาเป็นมะเร็งของรังไข่และมดลูกชนิดอะดีโนคาร์ซิโนมา ส่วนปัจจัยเสี่ยงอย่างอื่นไม่พบความแตกต่างกันในผู้ป่วยที่ตรวจพบลิ่มเลือดในหลอดเลือดดำชั้นลึกของขา และผู้ป่วยที่ตรวจไม่พบลิ่มเลือดในหลอดเลือดดำชั้นลึกของขา*

สรุป: *ความชุกของภาวะลิ่มเลือดอุดหลอดเลือดดำชั้นลึกของขาในผู้ป่วยมะเร็งนรีเวชในคนไทยพบได้สูง และผู้ป่วยมะเร็งของรังไข่และมดลูกที่ต้องเข้ารักษาโดยวิธีผ่าตัดมีความเสี่ยงสูงที่จะเกิดภาวะหลอดเลือดดำชั้นลึกของขาอุดจากลิ่มเลือด*